Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 2012;366:399-408. DOI: 10.1056/NEJMoa1111961.

List of Supplementary Appendices

Supplementary Appendix 1: Table 1 - Required Pre-randomization Evaluations and Investigations

	INVESTIGATIONS	TIMING
History and Physical Exam including:	Height and weight, performance status Presence/absence of "B" symptoms Presence/absence (and dimensions) of palpable adenopathy, and hepato-splenomegaly	**within 21 days prior to randomization**
Hematology	CBC, WBC differential, platelets ESR (Westergren method should be used)	
Biochemistry	Serum creatinine AST or ALT Alkaline phosphatase LDH Total Bilirubin Pregnancy test (if clinically indicated)	
Radiology*	Chest Xray PA and lateral	within 28 days prior to randomization
	CT of chest CT of abdomen and pelvis Bipedal lymphangiogram (if CT of abd/pelvis is negative) is strongly recommended. (It will not be mandatory if a local centre's practice is not to do LAGs.) Other studies as indicated i.e. sinus, skeletal, gastro-intestinal Gallium scan**	**within 8 weeks prior to randomization**
Other Investigations	Bone marrow aspirate and biopsy is recommended but must be done if blood counts abnormal*** Pulmonary function tests (if indicated - see section 5.1.3)	**within 8 weeks prior to randomization**
Quality of Life	EORTC QLQ-C30+3	within 14 days prior to randomization
Toxicity	Baseline "toxicity" evaluation (to document baseline symptoms)	

* To ensure compatibility baseline and subsequent xrays/scans to assess response must be performed using identical techniques

** Gallium scans are optional but if a disease site is identified by gallium, this must be indicated.

*** Abnormal defined as hemoglobin < 100 g/L women **(< 10.0 g/dl U.S.)**
< 120 g/L for men **(< 12.0 g/dl U.S.)**
WBC < 4.0×10^9/L **(< 4.0 x 10^3/µL U.S.)**

Supplementary Appendix 2: Summary of Patient Eligibility Requirements and Risk Stratification

Eligibility: Eligible patients were older than 15 years with previously untreated, histologically-confirmed, stage I-IIA non-bulky Hodgkin's lymphoma as defined using principles of the Ann Arbor classification[1]. Bulky adenopathy was defined as a palpable nodal mass greater than 10 cm. in diameter or a mediastinal mass with a maximum diameter measuring at least one-third of the maximum chest wall diameter. Patients with subdiaphragmatic disease located in the ileo-femoral, inguinal or para-iliac nodes were eligible. Patients with stage IA disease and all of lymphocyte predominant or nodular sclerosing histology, disease bulk less than 3 cm, erythrocyte sedimentation rate (ESR) less than 50, and unilateral high-neck or isolated epitrochlear adenopathy were considered to have very low-risk disease and were ineligible as it was then believed these patients might be successfully treated with IFRT. Also ineligible were those with intra-abdominal Hodgkin's lymphoma, lung or cardiac dysfunction, or other medical problems that precluded protocol therapy; abnormal baseline laboratory values of hematologic, renal or liver function; a known positive HIV antibody test; a prior or concurrent malignancy; and, having undergone a staging laparotomy. Before randomization, patients were assessed by a hematologist or medical oncologist and a radiation oncologist with both agreeing that protocol therapy could be safely administered.

Risk Stratification: Before randomization, patients were stratified into favorable and unfavorable risk cohorts and by treatment center. Prognostic stratification was employed to identify patients who would be at greater risk of progressive Hodgkin's lymphoma if treated with radiation therapy alone. Together, the two patient strata have broader inclusion than the more recently described German Hodgkin's Study Group (GHSG) "early-stage" disease[2,3] and European Organization for Research and Treatment of Cancer (EORTC) stage I-II "favorable-risk" disease[4,5] categories. Our design reflects the uncertain benefits of combined modality therapy for these patients that existed in the early 1990's[2,6,7]. In HD.6, unfavorable-risk patients had any of age older than 39 years , an ESR of at least 50 mm/hr, mixed cellularity or lymphocyte deplete histology and four or more sites of disease. Favorable-risk patients had none of these factors. Our prognostic classification was based on previous descriptions of retrospective analyses describing pre-therapy characteristics associated with inferior disease control in cohorts treated with extended-field radiation therapy, often following staging laparotomy[9-11]. When our trial was conceived, we speculated that combined modality therapy for patients with risk factors would be beneficial; subsequent reports of other randomized trials led to new care standards of combined modality therapy for all patients with stage I-IIA non-bulky disease[2,6,7].

References for Supplementary Appendix 2

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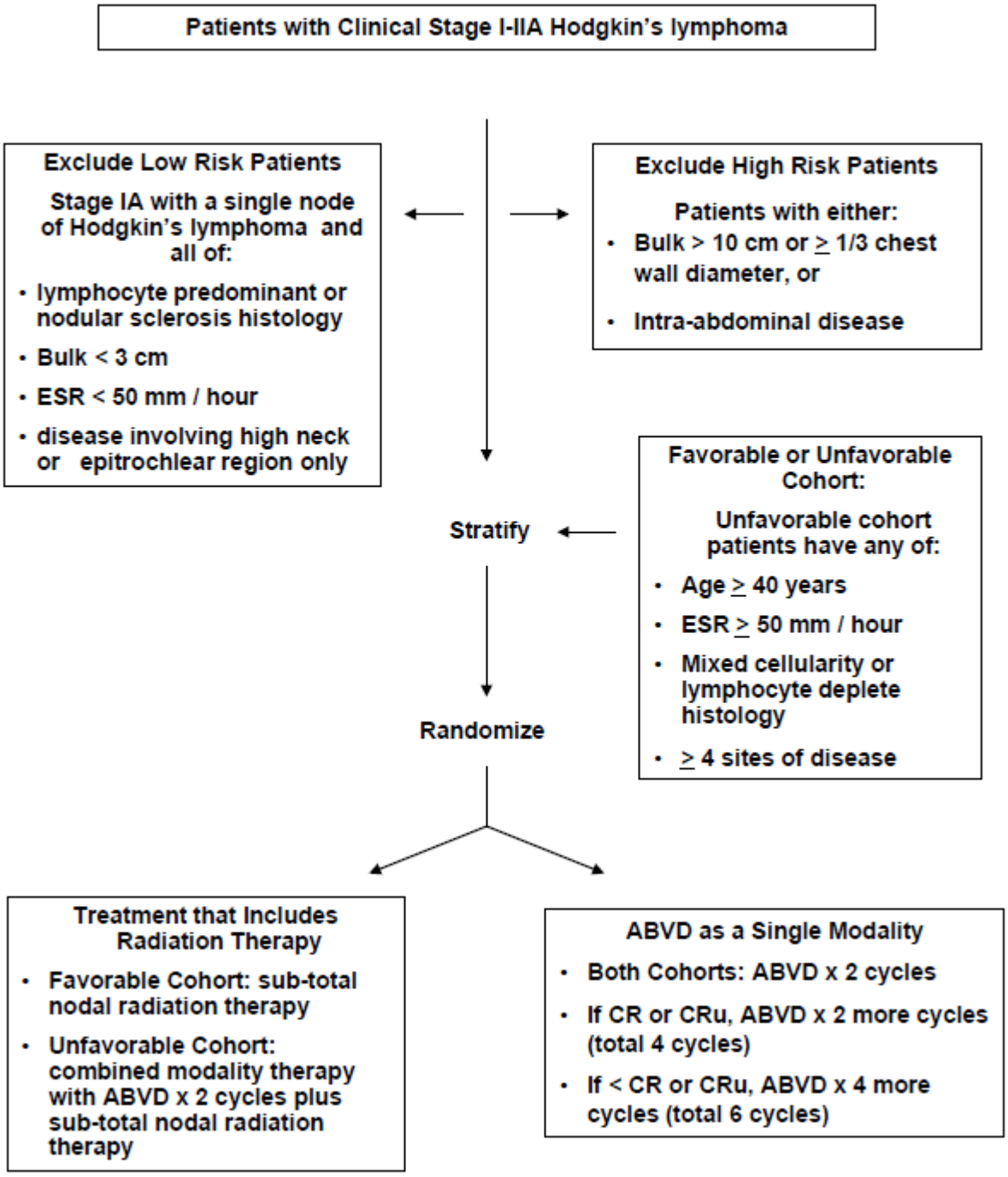
Supplementary Appendix 3: Figure 1- Study Schema



Previously reported in Meyer et al. J Clin Oncol 2005; 2005; 23: 4634-4642.

Supplementary Appendix 4: Summary of Radiation Therapy Details

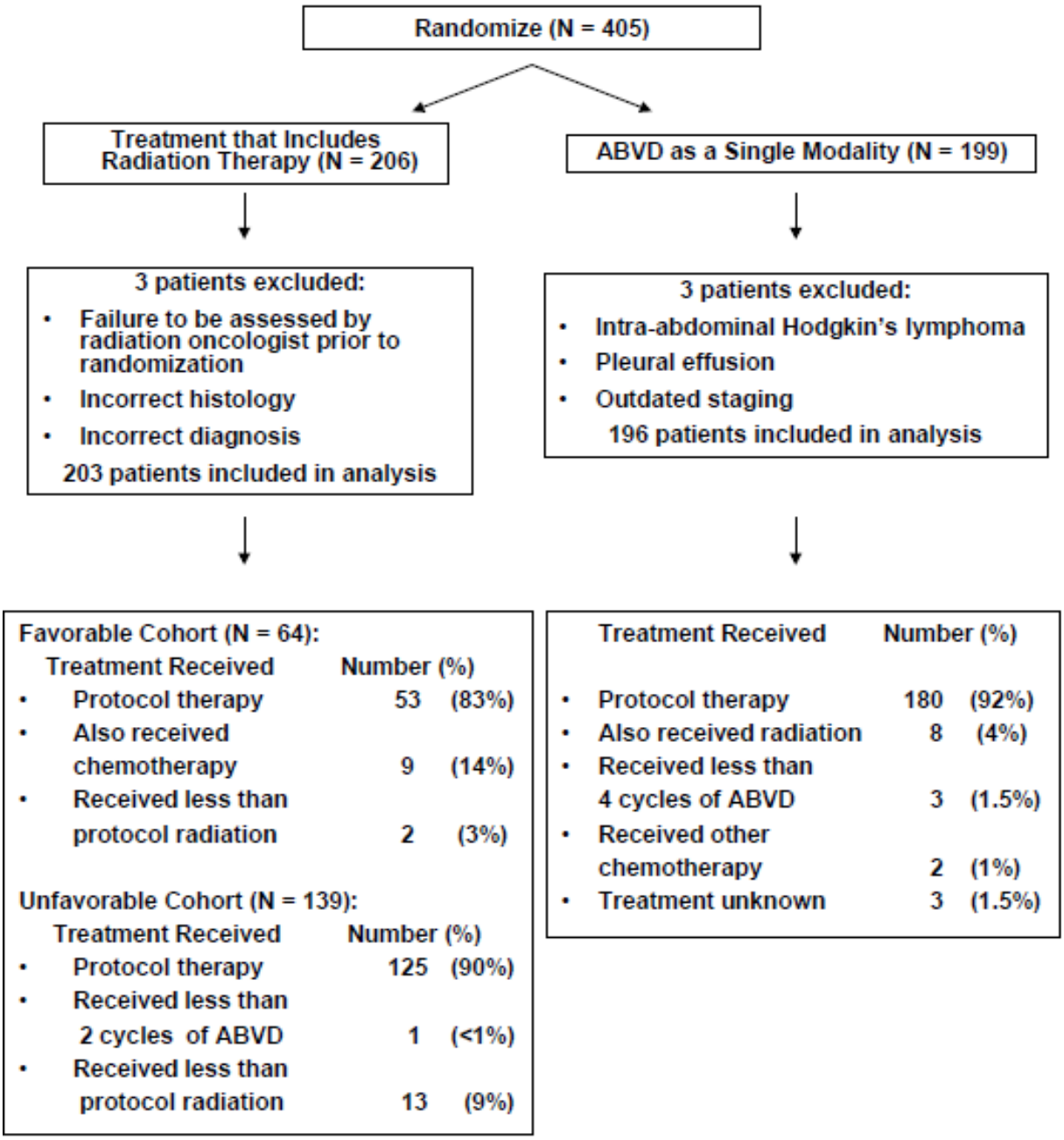
Favorable Cohort: These patients were treated with radiation therapy consisting of 35 Gy given in 20 daily fractions to supradiaphragmatic lymph node areas (mantle region) and 35 Gy given in 20 daily fractions to the spleen and para-aortic lymph nodes (to the level of L4).

Unfavorable Cohort: These patients received initial treatment with 2 cycles of ABVD. Radiation treatment commenced no earlier than 4 weeks and no later than 6 weeks after completion of chemotherapy. This delay was to minimize risks of cardiovascular toxicity related to doxorubicin. Neutrophil and platelet counts must have recovered (defined as a neutrophil count of $> 1.5 \times 10^9$/L and a platelet count of $> 125 \times 10^9$/L) prior to starting radiation. If this recovery required more than 6 weeks, radiation treatment was delayed. Radiation therapy consisted of 35 Gy given in 20 daily fractions administered to supradiaphragmatic lymph node areas (mantle region) and simultaneously to the spleen and upper abdominal lymph nodes to the level of L2. Alternatively, radiation therapy could be given consisting of mantle (35 Gy in 20 fractions) followed by separate radiation to the spleen and upper abdominal lymph nodes to the level of L2 (35 Gy in 20 fractions).

Note: Patients with subdiaphragmatic Hodgkin's lymphoma located in the ileo-femoral, inguinal or para-iliac nodes (i.e., isolated pelvic disease) received radiation therapy consisting of 35 Gy given in 20 fractions to an "inverted Y" field. The spleen was not radiated.

There was a centralized quality assurance process for review of radiation therapy prescriptions prior to treatment initiation.

Supplementary Appendix 5: Figure 2 - CONSORT Diagram



Previously reported in Meyer et al. J Clin Oncol 2005; 2005; 23: 4634-4642.

Supplementary Appendix 6: Table 2 - Pre-therapy Characteristics of Patients with Stage I-IIA Non-bulky Hodgkin's Lymphoma Treated with ABVD Alone or with a Strategy that Includes Radiation Therapy

Characteristic	ABVD Alone	With Radiation Therapy
Age at Randomization		
< 40 years	126 (64)	112 (55)
≥ 40 years	70 (36)	91 (45)
Median (years)	35	36.7
Gender		
Female	90 (46)	87 (43)
Male	106 (54)	116 (57)
Stage at Diagnosis		
IA	65 (33)	66 (33)
IIA	131 (67)	137 (67)
Histology		
Interfollicular	2 (1)	0 (0)
Lymphocyte Predominant	20 (11)	22 (11)
Nodular Sclerosis	133 (68)	131 (65)
Mixed Cellularity	41 (21)	47 (23)
Unclassified	0 (0)	3 (1.5)
Erythrocyte Sedimentation Rate		
< 50 mm/hr	165 (84)	177 (87)
≥ 50 mm/hr	31 (16)	26 (13)
Number of Involved Nodal Sites		
< 4	166 (85)	186 (92)
≥ 4	30 (15)	17 (8)
Prognostic Cohort*		
Favorable	59 (30)	64 (32)
Unfavorable	137 (70)	139 (68)

* Prior to randomization, patients were stratified into favorable and unfavorable risk cohorts. Favorable patients had all of the following characteristics: age less than 40 years; ESR less than 50 mm/hr; lymphocyte predominant or nodular sclerosing histology; and, fewer than four nodal sites of Hodgkin's lymphoma. Patients without any one or more of these characteristics were categorized into the unfavorable cohort.

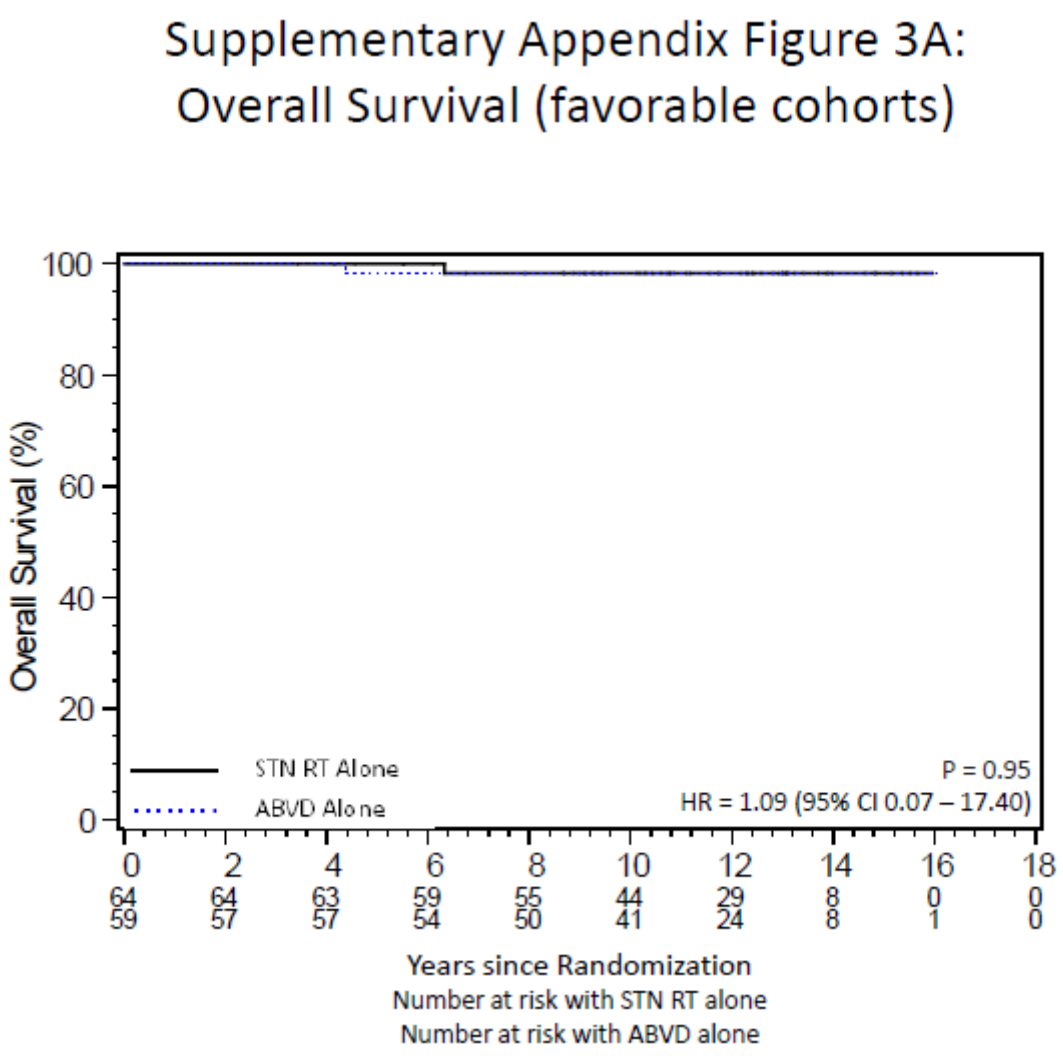
Supplementary Appendix 7: Table 3 - Follow-Up Details of Patients with Stage I-IIA Non-bulky Hodgkin's Lymphoma Treated with ABVD Alone or with a Strategy that Includes Radiation Therapy

	ABVD Alone N = 196 (%)	With Radiation Therapy N = 203 (%)	Total N = 399 (%)
Median follow-up duration (months)	135.7	135.0	135.1
Last status known between Jan. 1, 2009 and Dec. 31, 2010	128 (65)	134 (66)	262 (66%)
Alive	116 (59.2)	110 (54.2)	226 (56.6)
Dead	12 (6.1)	24 (20.7)	36 (9.0)
Last status learned after Dec. 31, 2010	39 (20)	42 (21)	81
Alive	38 (19.4)	42 (20.7)	80 (20.1)
Dead	1 (.5)	0 (0)	1 (.3)
Status unknown after Dec. 31, 2008	29 (14.8)	27 (13.3)	56 (14.0)

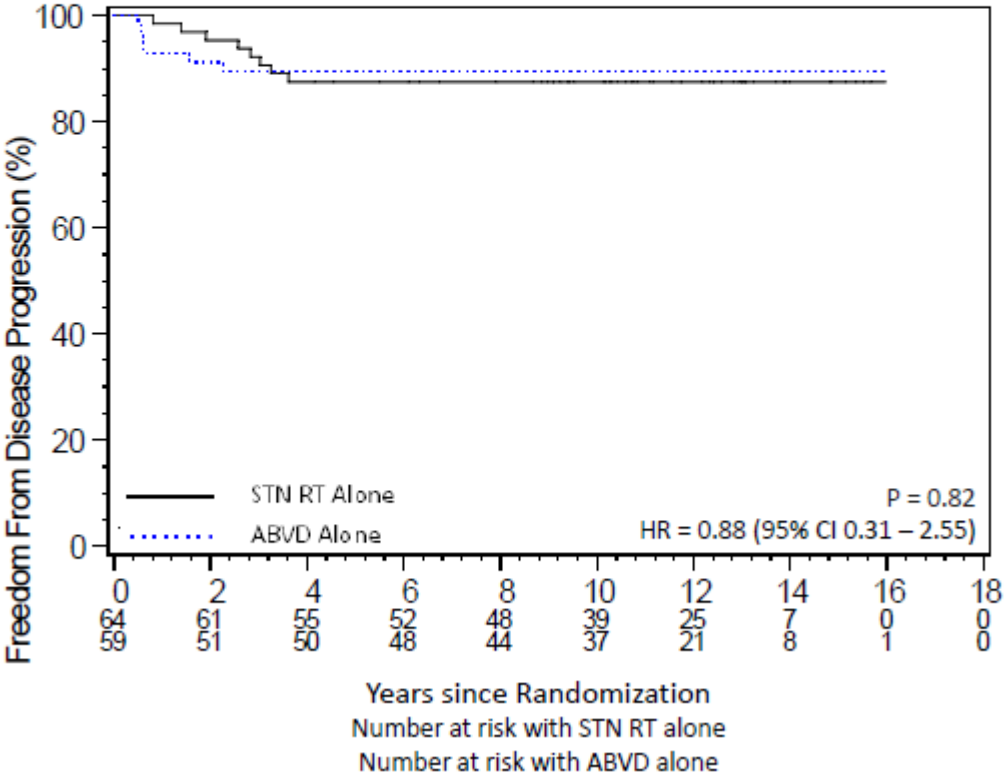
The clinical cut-off date for the final primary analysis of the HD.6 was predetermined to be December 31, 2010 and was based on the last known status of the patient at that time. The status of 81 patients was updated after December 31, 2010. A secondary sensitivity analysis was performed to include these data. No changes to conclusions were seen (See Supplementary Table 5).

Supplementary Appendix 8: Figure 3 - Kaplan–Meier Estimates of Overall Survival and Freedom from Progressive Disease among 123 Patients with Favorable-Risk Stage I-IIA Non-bulky Hodgkin's Lymphoma

Patients with favorable clinical features were randomly assigned to receive either doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) alone or subtotal nodal radiotherapy (STN RT). At 12 years, overall survival was 98% in those receiving ABVD alone and 98% in those receiving STN RT (Hazard Ratio [HR] = 1.09 [95% CI 0.07 – 17.4]; P = 0.95; Panel A) and freedom from progressive disease was 89% and 87% respectively (HR = 0.88 [95% CI 0.31 – 2.55]; P = 0.82; Panel B).

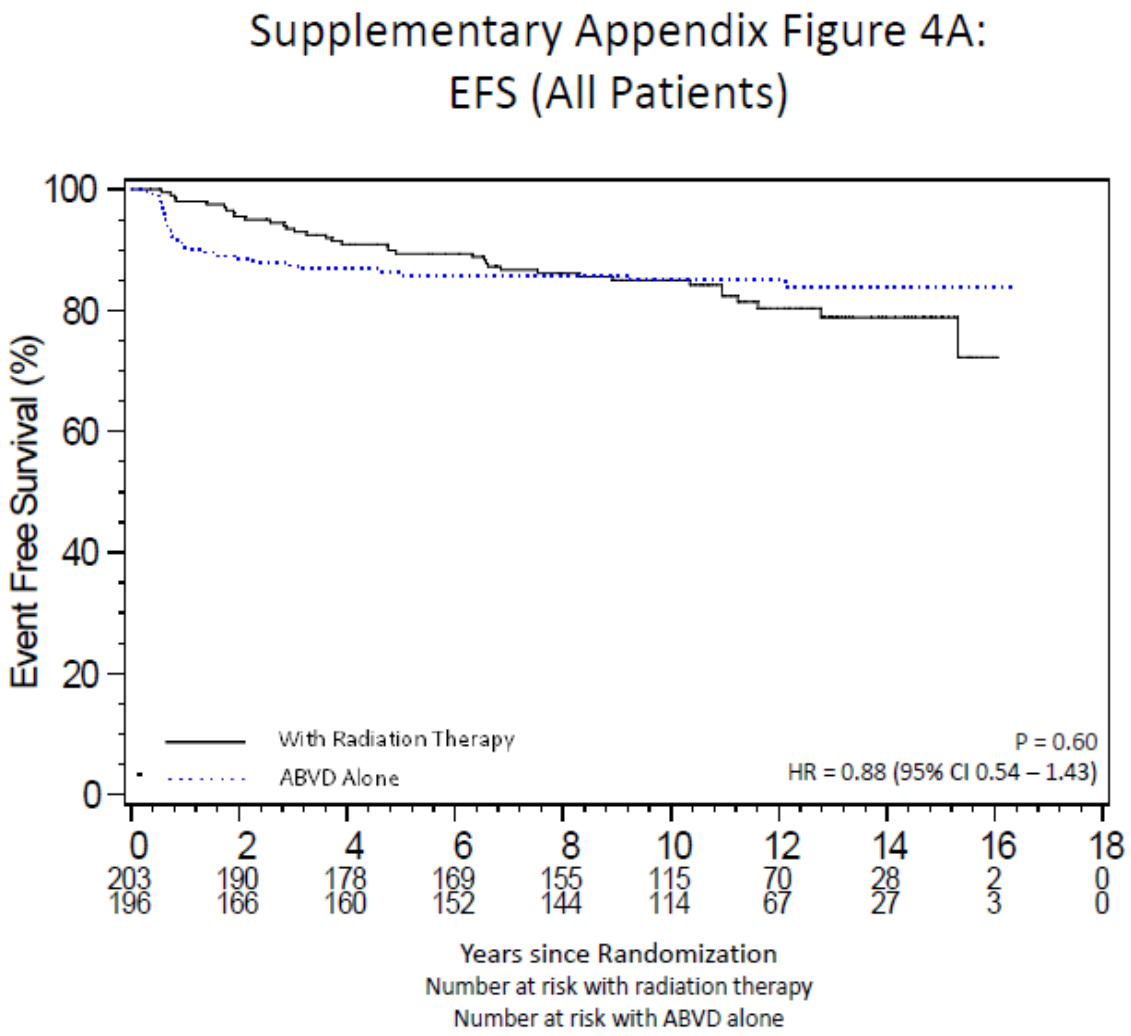


Supplementary Appendix Figure 3B: FFDP (favorable cohorts)

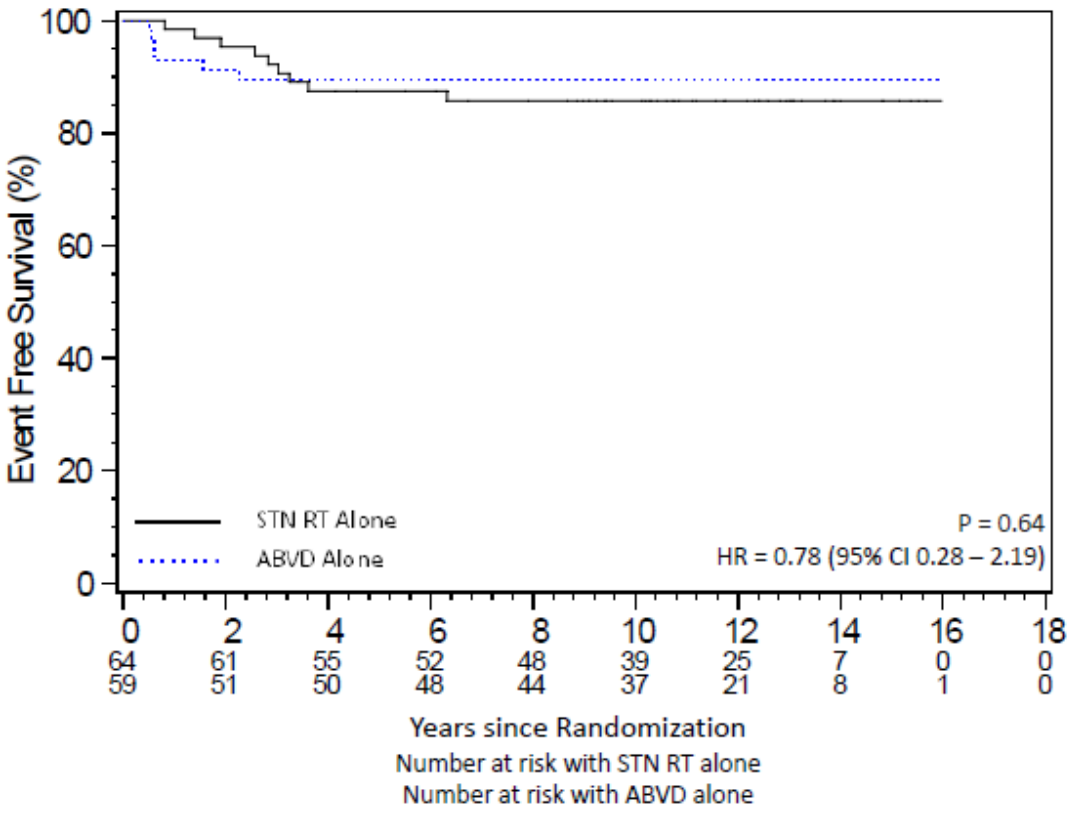


Supplementary Appendix 9: Figure 4 - Kaplan–Meier Estimates of Event-free Survival among 399 Patients with a Stage I-IIA Non-bulky Hodgkin's Lymphoma, Including by Risk Category

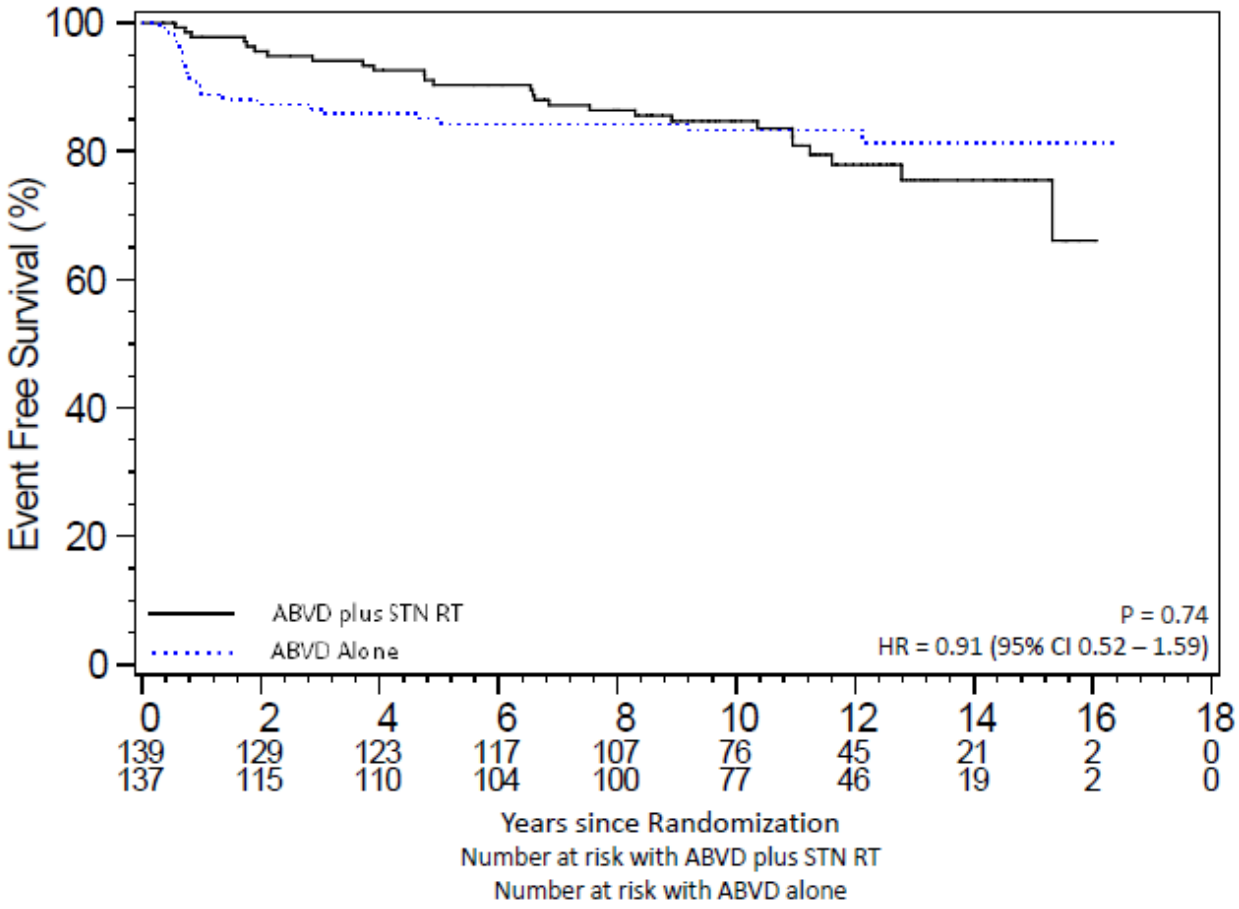
Patients were randomly assigned to receive either doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) alone or treatment that included subtotal nodal radiotherapy (STN RT). Among 203 patients allocated to STN RT, 64 had favorable-risk disease and received STN RT alone and 139 had unfavorable-risk disease and received two cycles of ABVD plus STN RT. In an analysis of all patients, at 12 years, event-free survival (EFS) was 85% and 80%, respectively (HR = 0.88 [95% CI 0.54 – 1.43]; P = .60; Panel A). The 12-year EFS among favorable-risk patients was 89% and 86% respectively (HR = 0.78 [95% CI 0.28 – 2.19]; P = .64; Panel B) and among unfavorable-risk patients was 83% and 78% respectively (HR = 0.91 [95% CI 0.52 – 1.59]; P = .74; Panel C).



Supplementary Appendix Figure 4B:
EFS (favorable cohorts)

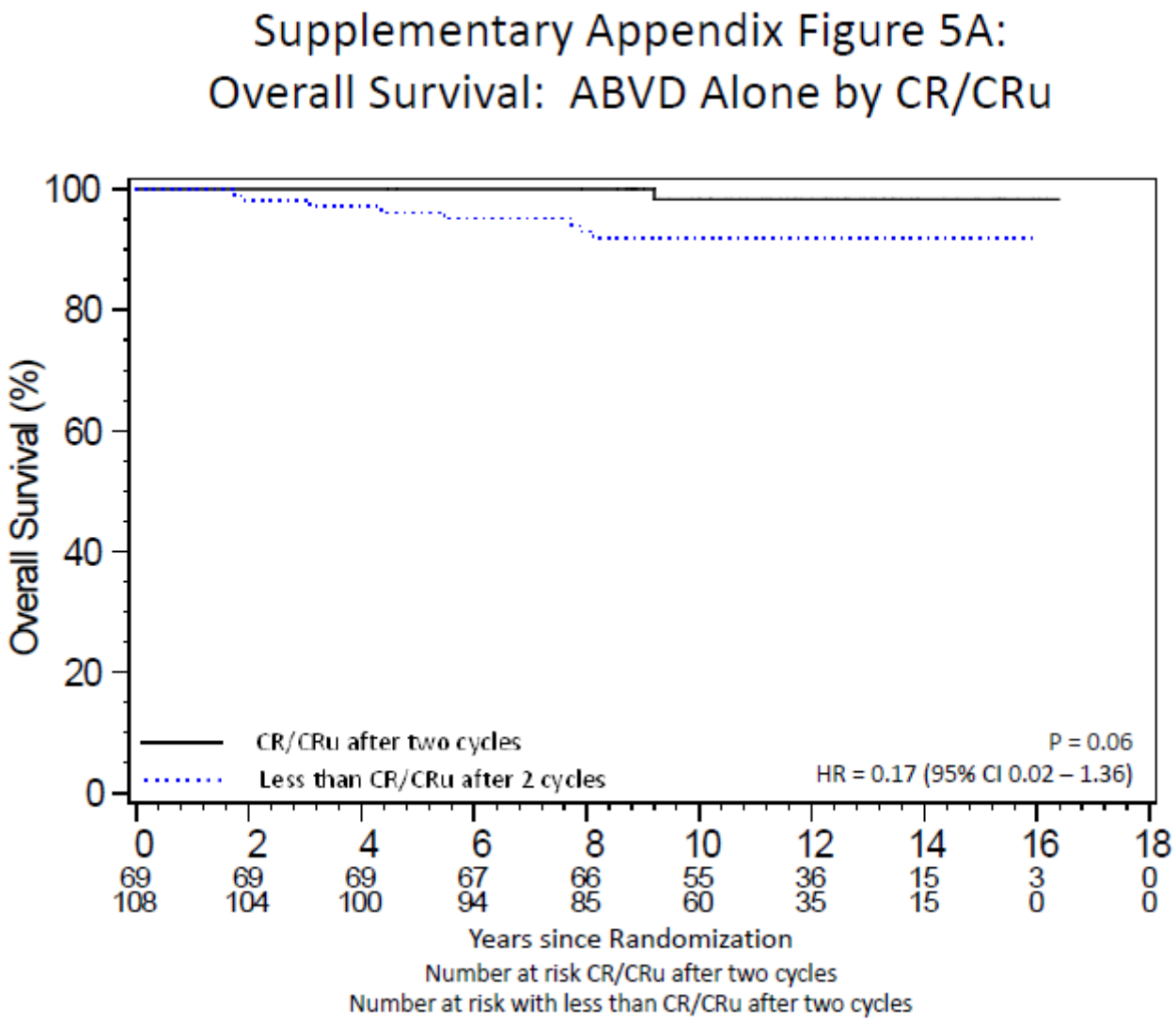


Supplementary Appendix Figure 4C:
EFS (unfavorable cohorts)

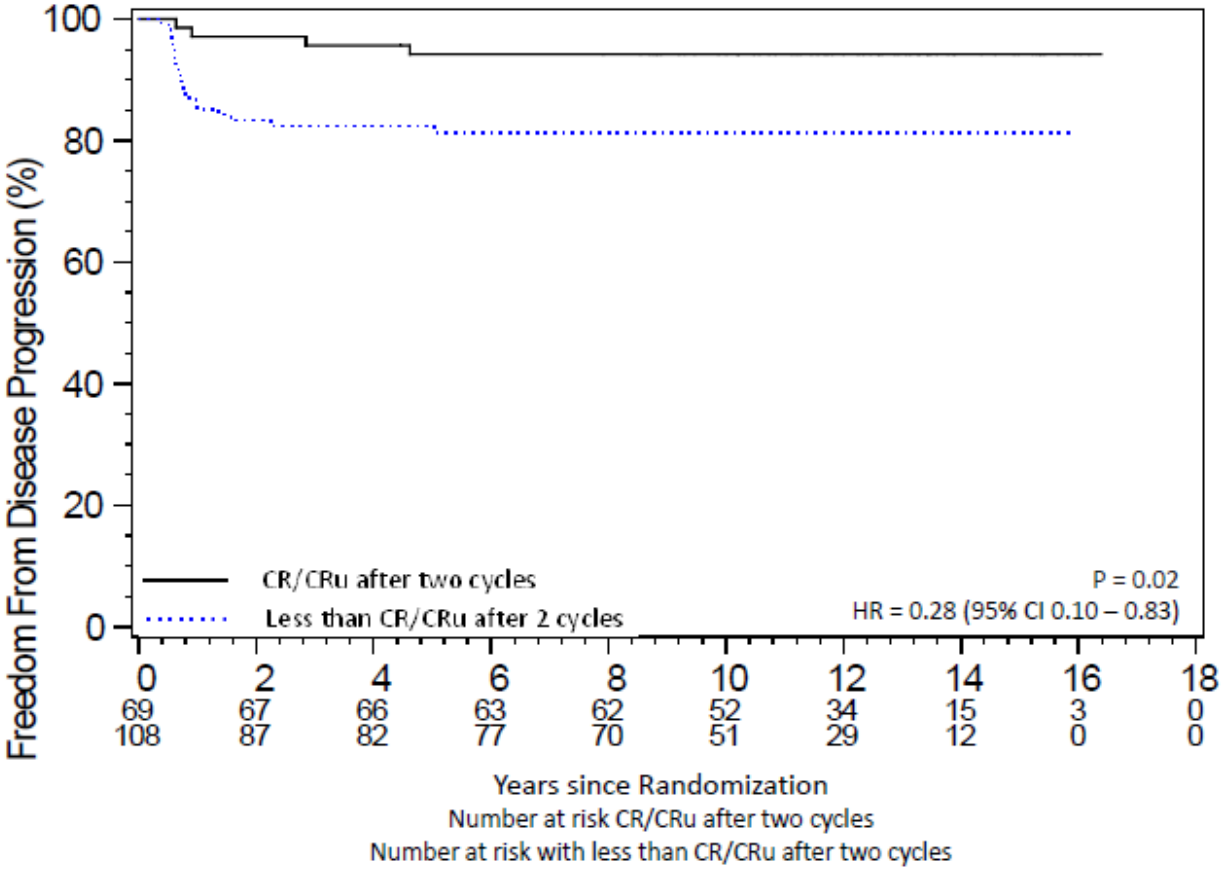


Supplementary Appendix 10: Figure 5 - Kaplan–Meier Estimates of Overall Survival and Freedom from Progressive Disease among 177 Patients with a Stage I-IIA Non-bulky Hodgkin's Lymphoma Treated with ABVD alone and Evaluable for Achievement of a Complete or Unconfirmed Complete Remission after Two Cycles of ABVD

Among 196 patients randomly assigned to receive doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) alone, 177 were evaluable for achievement of a complete (CR) or unconfirmed complete (CRu) remission after two cycles of ABVD. At 12 years, overall survival was 98% in 69 patients achieving CR/CRu and 92% in 108 patients who did not (Hazard Ratio [HR] = 0.17 [95% CI 0.02 – 1.36]; P = 0.06; Panel A) and freedom from progressive disease was 94% and 81% respectively (HR = 0.28 [95% CI 0.10 – 0.83]; P = 0.02; Panel B).



Supplementary Appendix Figure 5B:
FFDP: ABVD Alone by CR/CRu



Supplementary Appendix 11: Table 4 - Secondary Sensitivity Analysis of Outcomes of 405 Patients with Stage I-IIA Non-bulky Hodgkin's Lymphoma Treated with ABVD Alone or with a Strategy that Includes Radiation Therapy (Intent to Treat Analysis)

Patient Group	Outcome	ABVD Alone	With Radiation Therapy	Hazard Ratio* (95% Confidence Intervals)	P-value
All Patients N = 406		***N = 199***	***N = 206***		
	12-yr OS	94%	87%	0.49 (0.25 – 0.99)	0.04
	12-yr FFDP	87%	92%	1.99 (1.03 – 3.82)	0.04
	12-yr EFS	85%	81%	0.91 (0.56 – 1.47)	0.70
Favorable Cohort N = 125		***N = 60***	***N = 65***		
	12-yr OS	98%	98%	1.08 (0.07 – 17.27)	0.96
	12-yr FFDP	90%	88%	0.88 (0.31 – 2.54)	0.81
	12-yr EFS	90%	86%	0.78 (0.28 – 2.18)	0.63
Unfavorable Cohort N = 280		***N = 141***	***N = 139***		
	12-yr OS	92%	82%	0.47 (0.23 – 0.96)	0.04
	12-yr FFDP	86%	94%	3.42 (1.37 – 8.56)	0.009
	12-yr EFS	83%	78%	0.95 (0.55 – 1.65)	0.85

* Hazard Ratio considers experimental arm (ABVD alone) relative to control arm
OS: Overall survival; FFDP: Freedom from disease progression; EFS: Event-free survival

The primary analysis of the HD.6 trial includes all eligible patients, based on their pre-randomization characteristics. There were six ineligible patients (3 in each randomized group).

Supplementary Appendix 12: Table 5: Secondary Sensitivity Analysis of Outcomes of 399 Patients with Stage I-IIA Non-bulky Hodgkin's Lymphoma Treated with ABVD Alone or a Strategy that Includes Radiation Therapy (includes data obtained between the clinical cut-off and data-lock dates)

Patient Group	Outcome	ABVD Alone	With Radiation Therapy	Hazard Ratio* (95% Confidence Interval)	P-value
All Patients N = 399		***N = 196***	***N = 203***		
	12-yr OS	94%	87%	0.50 (0.25 – 1.00)	0.04
	12-yr FFDP	87%	92%	1.91 (0.99 – 3.69)	0.05
	12-yr EFS	85%	81%	0.88 (0.54 – 1.44)	0.61
Favorable Cohort N = 123		***N = 59***	***N = 64***		
	12-yr OS	98%	98%	1.09 (0.07 – 17.44)	0.95
	12-yr FFDP	89%	87%	0.88 (0.31 – 2.55)	0.82
	12-yr EFS	89%	86%	0.78 (0.28 – 2.19)	0.64
Unfavorable Cohort N = 276		***N = 137***	***N = 139***		
	12-yr OS	92%	82%	0.48 (0.23 – 0.98)	0.04
	12-yr FFDP	86%	94%	3.23 (1.28 – 8.13)	0.01
	12-yr EFS	83%	78%	0.91 (0.52 – 1.59)	0.75

* Hazard Ratio considers experimental arm (ABVD alone) relative to control arm
OS: Overall survival; FFDP: Freedom from disease progression; EFS: Event-free survival

The clinical cut-off date for the final primary analysis of the HD.6 was predetermined to be December 31, 2010 and was based on the last known status of the patient at that time. The status of 81 patients was updated after December 31, 2010. This secondary sensitivity analysis includes these data. The data-lock date was July 15, 2011.

Supplementary Appendix 13: Participating Centres and Investigators

Canadian Institutions: ***Alberta:*** Cross Cancer Institute, Edmonton; Tom Baker Cancer Centre, Calgary, Alberta; ***British Columbia:*** BCCA - Vancouver Cancer Centre, Vancouver; BCCA - Vancouver Island Cancer Centre, Victoria; ***Manitoba:*** CancerCare Manitoba, Winnipeg; ***New Brunswick:*** Atlantic Health Sciences Corporation Saint John Regional Hospital, Saint John; The Moncton Hospital, Moncton; The Vitalite Health Network - Dr. Leon Richard Oncology Centre, Moncton; ***Newfoundland:*** Dr. H. Bliss Murphy Cancer Centre, St. John's; ***Nova Scotia:*** Izaak Walton Killam (IWK) Health Centre Division of Pediatric Hematology-Oncology, Halifax; ***Ontario:*** Algoma District Cancer Program Sault Area Hospital, Sault Ste. Marie; Credit Valley Hospital, Mississauga; Humber River Regional Hospital, Toronto; Juravinski Cancer Centre at Hamilton Health Sciences, Hamilton; London Health Sciences, London; Mount Sinai Hospital, Toronto; Niagara Health System, St. Catharines; Regional Cancer Program of the Hopital Regional de Sudbury Regional Hospital, Sudbury; Thunder Bay Regional Health Science Centre, Thunder Bay; University Health Network-Princess Margaret Hospital, Toronto; ***Quebec:*** CHUM - Hopital Notre-Dame, Montreal; Hopital Maisonneuve-Rosemont, Montreal; McGill University - Dept. Oncology, Montreal; ***Saskatchewan*****:** Allan Blair Cancer Centre, Regina; Saskatoon Cancer Centre, Saskatoon.

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United States Main Institutions and Sites: ***Albert Einstein College of Medicine:*** Stony Brook University Medical; ***Case Western-MetroHealth Medical Center:*** Akron City Hospital; Aultman Hospital; University Hospitals of Cleveland; ***Colorado Cancer Research Program:*** Medical Center of Aurora; Presbyterian/St Luke's Medical Center; Swedish Medical Center; ***Drexel University College of Medicine:*** Blair Medical Associates; ***Indiana University Cancer Center:*** Central Indiana Cancer Centers; Illinois Masonic Medical Center; Indiana University Health Arnett Cancer Care; ***Johns Hopkins University:*** Central Pennsylvania Hematology & Medical Oncology Associates; ***Kalamazoo CCOP:*** West Michigan Cancer Center; ***Main Line Health CCOP:*** Paoli Memorial Hospital; ***Marshfield CCOP:*** Marshfield Clinic; ***Mayo Clinic:*** Cedar Rapids Oncology Associates; Creighton University Medical Center; Duluth Clinic; Flower Memorial Hospital; Illinois Oncology Research Associates; Iowa Methodist Medical Center; Mayo Clinic; Mayo Clinic in Arizona; Medcenter One Health Systems; Pennsylvania State Cancer Institute; Rapid City Regional Hospital; Sanford Clinic; Sanford Medical Center-Fargo; St

Joseph Mercy Hospital - Ann Arbor, Michigan; Toledo Clinic Cancer Centers-Toledo Clinic; ***Medical College of Wisconsin:*** Medical College of Wisconsin; ***Metro-Minnesota CCOP:*** Fairview-Southdale Hospital; Mercy Hospital; Park Nicollet Health Services; ***Northwestern University:*** Edward Kaplan and Associates; Evanston CCOP-NorthShore University; Fairview University Medical Center (Riverside, CA); Hematology-Oncology Associates-Melrose Park; Ingalls Medical Center; Northwestern University; Regions Hospital; ***Ochsner CCOP:*** Ochsner Clinic; ***University of Pennsylvania:*** Baptist Medical Center; Mercy Hospital – Scranton; University of Pennsylvania, St Luke's Hospital; ***University of Pittsburgh:*** DuBois Reg Med Center; ***University of Rochester:*** New York Oncology Hematology P.C.; Oncology/Hematology Consultants; University of Rochester; ***Rush University Medical Center:*** St John's Hospital; ***Stanford University:*** Memorial Medical Center; ***Tufts Medical Center:*** The Hospital of Central Connecticut; Tufts Medical Center; ***University of Pretoria:*** University of Pretoria; ***University of Florida-Jacksonville Health Science Center; Vanderbilt University; University of Wisconsin:*** Aspirus Regional Cancer Center; Dean Hematology and Oncology Center; St. Vincent Hospital Regional Cancer Center; Swedish American Hospital; ***West Virginia University.***

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Supplementary Appendix 14: Acknowledgements

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